Remarks

Claims 1-138 are pending. Claims 137 and 138 have been withdrawn from consideration as being drawn to a non-elected invention.

Summary of Interview

Applicant would like to thank the Examiner for her comments during the interview of August 11, 2005. Regarding the obviousness rejection of the claims, the Examiner indicated her position (that Lizardi discloses a rolling circle replication method involving decoupling of amplification target circles from the reporter binding molecule (open circle probe) effected by disrupting the base-pairing by exonuclease digestion or by heat denaturation) is based on the broad definition of decoupling in the present application. Applicants acknowledged that, broadly defined, "decoupling" can be achieved via a range of techniques, but also noted that, as claimed, decoupling refers to the release of an amplification target circle from a reporter binding molecule, not degradation of an open circle probe.

The Examiner also indicated that it was her position that the open circle probes of Lizardi are equivalent to the claimed reporter binding molecules. Applicants indicated that open circle probes are not amplification target circles. Applicants also indicated that there is no disclosure in Lizardi of where the OCP is either part of or dissociated from anything that could be considered a reporter binding molecule as claimed and therefore Lizardi cannot teach the dissociation of something that is never disclosed.

Rejection Under 35 U.S.C. § 103

Claims 1-136 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kingsmore et al. (U.S. Pat. No. 6,531,283) in view of Lizardi (U.S. Pat. No. 5,854,033). Applicants respectfully traverse this rejection.

Applicants submit the present rejection is based on misinterpretations of Lizardi and of the claimed method. Lizardi does not disclose what is alleged in the Office Action and, as a result, the combination of Kingsmore et al. and Lizardi do not disclose or suggest what is

presently claimed. In addition, there is no teaching, motivation or suggestion to combine the teachings of Kingsmore et al. and Lizardi to achieve the subject matter of the current claims. These errors render the rejection legally flawed with the result that the Office Action fails to establish a prima facie case of obviousness.

Applicants submit that, even considered together, Kingsmore et al. and Lizardi fail to disclose and suggest every feature of the claimed method. Applicants also submit that statements in the Office Action to the effect that "Lizardi teach decoupling of ATC from unligated open circle probes (reporter binding molecules)" are incorrect. Lizardi included no such disclosure and cannot be interpreted as making such a disclosure, and the Office Action fails to address these points which were carefully pointed out in the Response filed April 25, 2005. Applicants also submit that even if those of skill in the art were motivated to include the degradation step of Lizardi in the method of Kingsmore et al. (they would not be), such a combination would not produce the presently claimed method.

In making a determination of obviousness under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that (1) the prior art suggests the invention developed, and (2) the prior art indicates that the invention would have a reasonable likelihood of success. *See In re Dow Chem. Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). In order for a reference to be effective prior art under 35 U.S.C. § 103, it must provide a motivation whereby one of ordinary skill in the art would be led to do that which the applicant has done. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). The Patent Office has the burden under § 103 to establish a *prima facie* case of obviousness, which can be satisfied only by showing some objective teaching in the prior art would lead one to combine the relevant teachings of the references. *See In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). The present rejection does not meet this burden.

1. Before turning to the substance of this argument, Applicants first note that the Office Action (page 11) improperly disregarded Applicants' prior arguments on the grounds that

Applicants allegedly argued Kingsmore et al. and Lizardi separately. It is important to note that although it is a basic tenet of the law of obviousness that references should not be argued separately, this prohibition relates to situations where the combined teachings of the cited art disclose every claimed feature. This is not the case here, and as the cases cited above show, the combined teachings of the cited art must together disclose every claimed feature. From this, it is clear that it cannot be improper for applicants to point out that each cited publication fails to disclose one or more of the claimed features. Doing so does not become improper simply because applicants happen to point out such failings "separately" for each cited publication. Because Applicants properly pointed out that neither Kingsmore et al. nor Lizardi disclose or suggest decoupling of amplification target circles from their associated reporter binding molecules prior to replication of the amplification target circles, Applicants respectfully request reconsideration of Applicants prior arguments as well as the arguments below.

2. Kingsmore et al. discloses a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. Kingsmore et al. fails to disclose decoupling of the amplification target circle from the reporter binding primers. In fact, in the method of Kingsmore et al., the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication (see the bottom panels of Figure 1 where the amplification target circle is shown at the growing tip of the replicated strand).

Lizardi discloses a method of amplifying or detecting nucleic acids by target-mediated ligation of linear open circle probes (to form circular amplification target molecules) followed by amplification of the amplification target circles by rolling circle amplification (see from column

2, line 53, to column 3, line 7). The cited portions of Lizardi disclose a method of digesting and eliminating unligated open circle probes (OCPs) and gap oligonucleotides from the reaction when nested ligation mediated rolling circle amplification (LM-RCA) is to be performed. For example, Lizardi discloses that unligated OCPs associated with TS-DNA can be digested with an exonuclease to prevent them from interfering with nested LM-RCA (see, for example, column 24, lines 41-67). Lizardi fails to disclose or suggest digestion, dissociation or separation of amplification target circles from an associated reporter binding molecule prior to replication of the amplification target circles.

Thus, neither Kingsmore et al. nor Lizardi disclose or suggest decoupling of amplification target circles from their associated reporter binding molecules prior to replication of the amplification target circles. Kingsmore et al. and Lizardi, either alone or in combination, fail to disclose or suggest every feature of the claims. Accordingly, for at least these reasons, Kingsmore et al. and Lizardi fail to make obvious claims 1-136.

3. As claimed, the reporter binding molecules comprise a specific binding molecule and an amplification target circle. That is, the claimed reporter binding molecules include as a component an amplification target circle. After the specific binding molecule portion of the reporter binding molecule interacts with its cognate analyte, the amplification target circle that is part of that reporter binding molecule is decoupled from the reporter binding molecule. The decoupled amplification target circle is then replicated. Thus, the claims require at least (1) a reporter binding molecule that includes both a specific binding molecule (that can interact with an analyte) and an amplification target circle, (2) decoupling of that amplification target circle from that reporter binding molecule, and (3) replication of the decoupled amplification target circle.

The rejection equates materials disclosed in Lizardi and Kingsmore et al.; alleging that they correspond to certain claimed materials. In particular, the rejection appears to equate the unligated open circle probes of Lizardi with the claimed reporter binding molecules and/or with the claimed amplification target circles. The present claims require that the amplification target

circle and the reporter binding molecule have particular, recited features and that the amplification target circle and reporter binding molecule be manipulated in particular, recited ways. Applicants submit that the prior art must disclose or suggest each of the claimed materials, each of the claimed features of those claimed materials, and each of the claimed manipulations of those claimed materials. The present rejection appears to focus only on the materials themselves and fails to account for inconsistencies between the functions and manipulations of the materials pointed to in Lizardi and Kingsmore et al. and the functions and manipulations of the claimed materials. As a result, the present rejection is both confusing and fails to come close to making a prima facie case of obviousness. Accordingly, for at least these reasons, Kingsmore et al. and Lizardi fail to make obvious claims 1-136. If the present rejection is maintained, Applicants request that the Examiner point out exactly how the materials in Lizardi and Kingsmore et al. cited in the rejection are disclosed in Lizardi and Kingsmore et al. to have all of the properties required by the claims and to be manipulated in all of the ways required by the claims.

4. The present rejection asserts (page 7) that Lizardi discloses "that the method comprises decoupling amplification target circle from the reporter binding molecule (open circle probe)," and refers to exonuclease digestion of unligated open circle probes and heat denaturation of primers for support. Applicants carefully pointed out in their response mailed April 25, 2005 that the cited portions of Lizardi (describing exonuclease digestion of unligated open circle probes and heat denaturation of primers) do not in any way disclose or suggest decoupling of an amplification target circle from its associated reporter binding molecule. In response to Applicants' arguments, the Office Action notes (page 11) that the "instant specification defines decoupling as to [sic] physical disunion of one molecule of the component from another" and concludes from this that Lizardi "does teach such decoupling of ATC from unligated open circle probes (reporter binding molecules)." It appears from this last statement that the Examiner is equating the unligated open circle probes of Lizardi with the claimed reporter binding molecules. This is incorrect, they are not equivalent.

Applicants initially note that the breadth of the term "decoupling" is not an issue. Applicants accept that this term is broadly defined in the specification. The issue is that the exonuclease digestion of unligated open circle probes and heat denaturation of primers in Lizardi do not constitute any teaching regarding amplification target circles or reporter binding molecules. This is the case regardless of how broadly or narrowly the term "decoupling" is defined. The cited passages relate to degradation of unligated open circle probes (which are not amplification target circles) and heat denaturation of primers.

Regarding the rejection's equating the unligated open circle probes of Lizardi with the claimed reporter binding molecules, Applicants note that the unligated open circle probes of Lizardi cannot be equated to the claimed reporter binding molecules at least because the unligated open circle probes of Lizardi do not comprise an amplification target circle (that is, the unligated open circle probes of Lizardi do not have the properties that the claimed amplification target circles have). An amplification target circle is a circular DNA molecule (see page 19, lines 18-19 of the specification). An unligated open circle probe is a linear DNA molecule (see column 5, lines 22-23 of Lizardi). Thus, the unligated open circle probes of Lizardi are not amplification target circles and do not correspond to either an amplification target circle as claimed or a reporter binding molecule as claimed (the claimed reporter binding molecules comprise an amplification target circle). This is a critical distinction because, as a result of this distinction, the digestion of unligated open circle probes of Lizardi does not represent in any way decoupling of an amplification target circle from its associated reporter binding molecule, regardless of how decoupling is defined. Because of this gap in the teaching of Lizardi (combined with the admitted and corresponding gap in the teaching of Kingsmore et al.), the present rejection fails to cite art that discloses each and every claimed feature.

The Office Action also cites column 29, lines 12-22 as allegedly teaching decoupling of an amplification target circle from a reporter binding molecule. Specifically, the Office Action alleges that Lizardi teaches heat denaturation (rising the temperature to disrupt base-pairing) to decouple an amplification target circle from a reporter binding molecule. However, the cited

passage is actually drawn to the use of heat to disrupt the hairpin structure of a rolling circle replication primer in order to allow the primer to hybridize to an ATC. There is only a single molecule involved, therefore, there is no release of one molecule from another and certainly no disclosure of decoupling an amplification target circle from a reporter binding molecule.

The claimed method also requires replication of the amplification target circles after they are decoupled from the reporter binding molecules. As can be seen from the discussion above, and as is apparent from Lizardi, the unligated open circle probes that are digested (that is, destroyed) in Lizardi are never replicated in the method of Lizardi. In fact, the unligated open circle probes of Lizardi are destroyed by Lizardi specifically to prevent such unligated open circle probes from affecting replication of amplification target circles. Thus, the digested unligated open circle probes of Lizardi cannot constitute or suggest the claimed amplification target circles because the unligated open circle probes of Lizardi are never replicated and cannot be replicated in the method of Lizardi. This is another reason the unligated open circle probes of Lizardi cannot represent the claimed amplification target circles or the claimed reporter binding molecules: the claimed amplification target circle is replicated but the unligated open circle probes are not cannot be replicated following their digestion. For at least these additional reason, Kingsmore et al. and Lizardi fail to disclose or suggest the method of claims 1-136. Accordingly, for all of the reasons above, Kingsmore et al. and Lizardi fail to make obvious the method of claims 1-136.

5. A rejection under 35 U.S.C. 103 cannot be sustained if the proposed modification would alter the fundamental principle of operation of the prior art to be modified. *In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349(CCPA 1959). Modification of the method of Kingsmore et al. cited in the rejection as suggested in the rejection would change the principle of operation of the method and thus the present rejection cannot be sustained.

Kingsmore et al. discloses a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte.

An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. In the method of Kingsmore et al. the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication.

In fact, if the amplification target circle was dissociated from the reporter binding primer prior to replication, the amplification target circle could not be replicated because such dissociation would separate the amplification target circle from the rolling circle replication primer (the primer is part of the reporter binding primer). Further, even if such a hypothetical dissociated amplification target circle was replicated using a different primer, this would defeat Kingsmore et al.'s purpose in having a rolling circle replication primer as part of a reporter binding primer. Kingsmore et al. states that:

> The method involves associating nucleic acid primer with the analyte and subsequently using the primer to mediate rolling circle replication of a circular DNA molecule. Amplification of the DNA circle is dependent on the presence of the primer. Thus, the disclosed method produces an amplified signal, via rolling circle amplification, from any analyte of interest. The amplification is isothermic and can result in the production of a large amount of nucleic acid from each primer. <u>The amplified DNA remains associated with the analyte, via the primer, and so allows spatial detection of the analyte.</u>

Column 4, lines 37-47 (emphasis added).

Dissociation of the amplification target circle would eliminate the intended connection between the analyte and the amplified DNA and thus eliminate the spatial detection of the analyte sought by Kingsmore et al. This alteration, required by the present rejection, would eliminate a major feature of the method of Kingsmore et al. Such a change in the principle of operation of the method of Kingsmore et al., which results from the modification proposed by the rejection, renders the rejection unsustainable. Accordingly, Kingsmore et al. and Lizardi fail to make obvious the method of claims 1-136.

Double Patenting Rejection

Claims 1, 12-113 and 118-136 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-72 of U.S. Patent No. 6,531,283 to Kingsmore et al. in view of U.S. Pat. No. 5,854,033 to Lizardi. Applicants respectfully traverse this rejection.

Applicants submit the present rejection is based on misinterpretations of Lizardi and of the claimed method. Lizardi does not disclose what is alleged in the Office Action and, as a result, the combination of the claims of Kingsmore et al. and Lizardi do not disclose or suggest what is presently claimed. In addition, there is no teaching, motivation or suggestion to combine the teachings of Kingsmore et al. and Lizardi to achieve the subject matter of the current claims. These errors render the rejection legally flawed with the result that the Office Action fails to establish a prima facie case of obviousness.

Applicants submit that, even considered together, Kingsmore et al. and Lizardi fail to disclose and suggest every feature of the claimed method. Applicants also submit that statements in the Office Action to the effect that "Lizardi teach decoupling of ATC from unligated open circle probes (reporter binding molecules)" are incorrect. Lizardi included no such disclosure and cannot be interpreted as making such a disclosure, and the Office Action fails to address these points which were carefully pointed out in the Response filed April 25, 2005. Applicants also submit that even if those of skill in the art were motivated to include the degradation step of Lizardi in the method of Kingsmore et al. (they would not be), such a combination would not produce the presently claimed method.

2. The claims of Kingsmore et al. disclose a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem

sequence DNA. Kingsmore et al. fails to disclose decoupling of the amplification target circle from the reporter binding primers. In fact, in the method of Kingsmore et al., the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication (see the bottom panels of Figure 1 where the amplification target circle is shown at the growing tip of the replicated strand).

Lizardi discloses a method of amplifying or detecting nucleic acids by target-mediated ligation of linear open circle probes (to form circular amplification target molecules) followed by amplification of the amplification target circles by rolling circle amplification (see from column 2, line 53, to column 3, line 7). The cited portions of Lizardi disclose a method of digesting and eliminating unligated open circle probes (OCPs) and gap oligonucleotides from the reaction when nested ligation mediated rolling circle amplification (LM-RCA) is to be performed. For example, Lizardi discloses that unligated OCPs associated with TS-DNA can be digested with an exonuclease to prevent them from interfering with nested LM-RCA (see, for example, column 24, lines 41-67). Lizardi fails to disclose or suggest digestion, dissociation or separation of amplification target circles from an associated reporter binding molecule prior to replication of the amplification target circles.

Thus, neither the claims of Kingsmore et al. nor Lizardi disclose or suggest decoupling of amplification target circles from their associated reporter binding molecules prior to replication of the amplification target circles. Kingsmore et al. and Lizardi, either alone or in combination, fail to disclose or suggest every feature of the claims. Accordingly, for at least these reasons, claims 1-72 of Kingsmore et al. and Lizardi fail to make obvious claims 1, 12-113 and 118-136.

As discussed in detail above in connection with the rejection under 35 U.S.C. § 103, Kingsmore et al. and Lizardi fail to disclose or suggest (1) a reporter binding molecule that includes both a specific binding molecule (that can interact with an analyte) and an amplification target circle, (2) decoupling of that amplification target circle from that reporter binding molecule, and (3) replication of the decoupled amplification target circle, all of which are

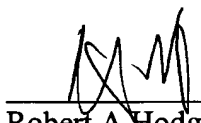
required by the present claims. Further, modifying the method of the claims of Kingsmore et al. would alter the fundamental principle of operation of the method of Kingsmore et al. For at least these reasons (as discussed above), claims 1-72 of Kingsmore et al. and Lizardi fail to make obvious claims 1, 12-113 and 118-136.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $455.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(1) and 1.17(e), and a Request For Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



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